Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 1-11, 13, 17, 19-30, 45-52, 54-66, 69, and 70 are pending in the application, with claims 1 and 45 being the independent claims. Claims 31 and 67 are sought to be cancelled without prejudice to or disclaimer of the subject matter therein.

Claims 1, 2, 5, 6, 9, 13, 45, 49, and 50 have been amended.

Claim 1 and 45 have been amended to recite "wherein the pluripotent cells are selected from the group consisting of embryonic stem (ES) cells, primordial germ (EG) cells and pluripotent adult stem cells." Support for the amendments is found throughout the specification and claims as originally filed, for example, in the specification at page 12, lines 6-8.

Claim 45 has further been amended to recite "wherein a 10 ml aliquot of a suspension in (ii) comprising 0.2 x 10^6 pluripotent cells yields sufficient EBs to seed six 20 ml suspensions each comprising 1000 EBs." Support for the amendment is found throughout the specification and claims as originally filed, for example, in the specification at Example 2 and Figure 1.

Claim 9 has been amended to depend from claim 1 instead of claim 8. Support for the amendment is found throughout the specification and claims as originally filed, for example, at original claims 1, 7, and 9.

Claims 2, 5, 6, 13, 49, 50 have been amended to correct clerical errors.

These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112, first paragraph

The rejection of claims 1-11, 13, 17, 19-31, 45-52, 54-67, 69 and 70 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement is respectfully traversed.

Claims 31 and 67 have been canceled rendering the rejection moot with regard to these claims.

The Office Action ("OA") acknowledges that the specification is "enabling for producing embryoid bodies (EBs) from pluripotent embryonic stem (ES) cells, embryonic germ (EG) cells or pluripotent non-embryonic stem cells[.]" OA, p. 2, ¶3. Solely to expedite prosecution, and not in acquiescence to the rejection, independent claims 1 and 45 have been amended to recite "wherein the pluripotent cells are selected from the group consisting of embryonic stem (ES) cells, primordial germ (EG) cells and pluripotent adult stem cells." Claims 1-11, 13, 17, and 19-30 depend from claim 1 and incorporate all of its elements; claims 46-52, 54-69, and 70 depend from claim 45 and incorporate all of its elements.

Applicants however respectfully submit that the specification enables the full scope of the claimed method for producing embryoid bodies (EBs) from pluripotent cells. The Office supports its allegation of lack of enablement by asserting that the phrase "pluripotent cells" can encompass cell types, *e.g.*, early primitive ectoderm-like cells, multipotent adult progenitor cells or adult neural stem cells, that have not yet been reported to form EBs. OA, pp. 5-6, bridging paragraph. Even assuming, *arguendo,* that the lack of reported EB formation by a cell is evidence of the cell's inability to form EB, the specification is still enabling because the presence of inoperative embodiments within the scope of a claim does not necessarily render a claim not enabled. M.P.E.P § 2164.08(b) (citing *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569 (Fed. Cir. 1984)). Rather, the standard is whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art. *Id.* As acknowledged by the Examiner, the specification is enabling for producing embryoid bodies (EBs) from pluripotent embryonic stem (ES) cells, embryonic germ (EG) cells or pluripotent non-embryonic stem cells. Thus, using the teachings applicable to these cells, the skilled artisan can determine whether a particular embodiment is operative or inoperative with expenditure of no more effort than is normally required in the art. Accordingly, Applicants respectfully assert that the claimed method is fully enabled.

Secondly, it is Applicants' understanding that the Office does not allege a lack of enablement for a method of culturing EBs under conditions allowing differentiation of the EBs into cardiomyocytes, and the rejection of claims 17, 19-31, 54-67, 69 and 70 under 35 U.S.C. § 112, first paragraph is solely supported by the fact that claims 17, 19-31, 54-67, 69 and 70 depend from claims 1 or 45. OA, p. 2, ¶3. Applicants' understanding is based on the lack of any stated reasons in the Office Action for an alleged lack of enablement for a method of culturing EBs under conditions allowing differentiation of the EBs into cardiomyocytes. However, Applicants reiterate that the specification is enabling for a method of culturing EBs under conditions allowing differentiation of the EBs into cardiomyocytes because one reasonably skilled in the art could do so without undue experimentation based on the disclosures of the specification coupled with information known in the art. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). The specification discloses working examples of a method of culturing EBs under conditions allowing differentiation of the EBs into cardiomyocytes. *See, e.g.,* specification, Examples 1 and 2. Additionally, as disclosed in the specification, methods to culture EBs under conditions that allow differentiation of the EBs into cardiomyocytes are known in the art. *See, e.g.,* specification, p. 2, ll. 6-15 and p. 17, ll. 28-32. Additional methods are disclosed, for example, in Dang *et al.*, U.S. Patent Appl. Publication No. 2003/0119107 ("Dang") and Kehat *et al.*, *The Journal of Clinical Investigation*, 108(3):407-414 (2001) ("Kehat"), both of which were cited in the outstanding Office Action.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112, first paragraph be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 112, second paragraph

The rejection of claims 9 and 10 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite is respectfully traversed.

The OA asserts that claim 9 is indefinite because claim 9 recites a time interval that is longer than the time interval recited in claim 8, from which claim 9 depends. OA, p. 7, ¶3. Solely to expedite prosecution, claim 9 has been amended to depend from claim 1. Claim 10 depends from claim 9 and incorporates all of its recitations.

Accordingly, Applicants respectfully request that the rejections under 35 U.S.C. § 112, second paragraph be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 102

The rejection of claims 31 and 67 under 35 U.S.C. § 102(e) as being anticipated by Dang is respectfully traversed.

Solely to expedite prosecution, claims 31 and 67 have been canceled.

Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) be reconsidered and withdrawn.

Rejections under 35 U.S.C. § 103

Applicants respectfully traverse the rejection of claims 45-52, 54-66, and 70 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Dang in view of Yan *et al.*, U.S. Patent Appl. Publication No. 2003/0027331 ("Yan") and Kehat.

In *KSR International v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007), the Supreme Court clarified the requirements for a proper obviousness analysis under 35 U.S.C. § 103(a). The Court noted that the analysis supporting a rejection under 35 U.S.C. § 103(a) should be made explicit, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the way the claimed new invention does." *Id.* at 1741. However, "[i]f [the] proposed modification would render the prior art invention being modified unsatisfactory for its intended purpose, then there is no suggestion or motivation to make the proposed modification. M.P.E.P. § 2143.01, Section V (citing *in re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

Additionally, at least some degree of predictability is required when determining that one of ordinary skill in the art would have a reasonable expectation of success. See M.P.E.P. § 2143.02 (II). Thus, unpredictability in the field of the invention can weigh against a finding of obviousness. *See In re Schecter*, 205 F.2d 185 (C.C.P.A. 1953).

Further, it is well-established that a prior art reference must be considered in its entirety (i.e., as a whole), including portions that would lead away from the claimed invention. *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540 (Fed. Cir. 1983). *See also* M.P.E.P. § 2141.02(VI).

Claim 45 is directed to a method for producing embryoid bodies (EBs) from pluripotent cells comprising: (i) obtaining a liquid single cell suspension culture of pluripotent cells; (ii) collecting and suspending the cells in a container to a density of about 0.1 x 10^6 to 1 x 10^6 cells/ml; (iii) rocking the container containing the liquid single cell suspension culture thereby generating cell aggregates; (iv) rocking the container containing the suspension until formation of EBs; wherein the pluripotent cells are selected from the group consisting of embryonic stem (ES) cells, primordial germ (EG) cells and pluripotent adult stem cells, and wherein a 10 ml aliquot of a suspension in (ii) comprising 0.2 x 10^6 pluripotent cells yields sufficient EBs to seed six 20 ml suspensions each comprising 1000 EBs. Claims 46-52, 54-66, and 70 depend from claim 45 and incorporate all of its elements.

Applicants respectfully submit that the rejected claims are not *prima facie* obvious over the cited art at least because (1) the cited art does not provide a skilled artisan with a reason or rationale to modify its teachings to arrive at the claimed invention and (2) the cited art does not provide the skilled artisan with a reasonable expectation of success when modifying its teachings to arrive at the claimed invention. *KSR International v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007).

One aspect of the invention is to provide a reliable, easy and cost-effective method for producing sufficient amounts of high quality embryoid bodies (EBs) suitable for use in high throughput screening (HTS) assays. Specification, p. 2, ll. 21-25. The claimed reliable, easy-to-use method yields 500-1000 EBs/ml from a 0.1-0.5 x 10^6 ES cells/ml starting suspension, wherein about 95% of the EBs show spontaneous beating cardiac cells. Schwengberg Declaration, section 11 (September 24, 2009). The methods for producing embryoid bodies known at the time of filing the captioned application either did not produce sufficient amounts of EBs or were cumbersome to use. Specification, p. 2, ll. 3-22. For example, the "stirring method," a method similar to the one disclosed in Dang, produces only half the number of EBs produced by the claimed method. Schwengberg Declaration, section 11.

Dang

The Office concedes that Dang does not teach, *inter alia*, a method for producing EBs comprising suspending cells in a container to a density of about 0.1 x 10^6 to 1 x 10^6

cells/ml, or rocking the container containing the liquid single cell suspension culture thereby generating cell aggregates, as recited in claim 45. Office Action ("OA"), p. 12, ¶2. Dang discloses *static* liquid suspension cultures (LSC), stirred cultures (SC), and encapsulated stirred cultures (ESC) for EB generation. *See, e.g.*, Dang, ¶162. Dang further discloses in Table 4 the EB efficiency of its liquid suspension cultures (LSC), stirred cultures (SC), and encapsulated stirred cultures (ESC) initiated with 10^3 and 10^4 ES cells/ml. Dang, Table 4. The stirred culture (SC) had the worst EB efficiency, >0.1%, at all starting cell concentrations. *Id.* Additionally, the EB efficiency of the LSC and ESC cultures declined with increasing starting ES cell concentration. *Id.*

A skilled artisan contemplating Dang would have had no reason or rationale to modify its teachings to arrive at the claimed method. First, a skilled artisan contemplating the declining EB efficiency of the LSC and ESC cultures with increased starting ES cell concentration would have had no reason to *further increase* the starting ES cell concentration to about 0.1×10^6 to 1×10^6 cells/ml as recited in claim 45. Second, Dang provides no reason or rationale for a skilled artisan to modify its *static* liquid suspension culture (LSC) to rock the container containing the liquid single cell suspension culture thereby generating cell aggregates. On the contrary, Dang discloses that "cells placed directly into stirred culture quickly aggregate into large cell clumps that did not proliferate or differentiate." Dang, ¶162. Dang also reports that the EB efficiency of the stirred SC culture is at least two orders of magnitude lower than the EB efficiency of the static LSC culture. Dang, Table 4. A skilled artisan contemplating the low EB efficiency of Dang's stirred SC culture would conclude that Dang teaches away from a method comprising rocking a liquid single cell suspension culture thereby generating cell aggregates. Third, Dang provides no reason or rationale for a skilled artisan to modify its *encapsulated* suspension cultures (ESC) so that the ES cells are capable to generate cell aggregates, as recited in claim 45. Dang discloses that

> the present inventors identified aggregation of embryonic stem cells and embryoid bodies (EBs) as the cause of the difficulty in generating large numbers of the embryonic stem cells (ES) cell-derived tissues. To counter this, the invention provides a novel bioprocess where aggregation of spheroid forming cells, such as embryonic stem cells and spheroids, such as EBs is controlled, such as by encapsulation of within a matrix. Dang, Abstract.

Dang also discloses that the stirred non-encapsulated SC culture has an EB efficiency that is at least two orders of magnitude lower than the EB efficiency of the ESC culture. Therefore, Dang provides no reason or rationale to modify its ESC culture to arrive at the claimed invention because a skilled artisan would have understood that the proposed modification, *i.e.*, removal of encapsulation to allow ES cell aggregation, would render the ESC culture unsatisfactory for its intended purpose. M.P.E.P. § 2143.01, Section V (citing *in re Gordon*, 733 F.2d 900 (Fed. Cir. 1984).

For at least the above discussed reasons, a skilled artisan also would have had no reasonable expectation of success when attempting to modify Dang's teachings to arrive at the claimed method that yields from a 10 ml aliquot of a single cell suspension comprising 0.2 x 10^6 pluripotent cells sufficient EBs to seed six 20 ml suspensions each comprising 1000 EBs. Rather, contemplating the reported 0.1% EB efficiency of Dang's stirred suspension culture (SC), the skilled artisan would have expected the claimed method to fail.

Yan

Yan does not remedy the deficiencies of Dang. Yan allegedly discloses "growing the HS cells [homozygous stem cells] in single cell suspension culture . . . and culturing the cells as suspension cells in suspension culture at a density of 1-3 x 10^6 cells to allow stem cells to form . . . embryoid bodies." OA, p. 12, ¶3 (citing Yan, ¶293). Yan, however, is silent regarding a method for generating EBs comprising, *inter alia*, rocking a container containing a liquid single cell suspension culture thereby generating cell aggregates. Therefore, the combination of Dang and Yan provides no reason or rationale for the skilled artisan to modify their teachings to arrive at the claimed invention. Additionally, Yan is void of any disclosure that would have provided the skilled artisan with a reasonable expectation of success when attempting to modify the teachings of the cited art to arrive at the claimed invention.

Kehat

Kehat also does not remedy the deficiencies of Dang. Kehat allegedly discloses that "ES cell clumps were grown in plastic petri dishes at a cell density of about 5 x 10^6 cells in a 58 mm dish." OA, p. 12, ¶4 (citing Kehat, p. 408, paragraph bridging left and right columns). Kehat, however, does not disclose a method comprising suspending cells

in a container to a density of about 0.1 x 10^6 to 1 x 10^6 cells/ml. Kehat only discloses that 5 x 10^6 cells were placed in a 58 mm dish. Without knowing the volume of the culture, a skilled artisan cannot determine the concentration of the cells. Additionally, Kehat is silent regarding a method comprising rocking a container containing a liquid single cell suspension culture thereby generating cell aggregates. Instead, Kehat discloses a method that uses *clumps* of ES cells as starting material. At least for these reasons, the combination of Dang and Yan provides no reason or rationale for the skilled artisan to modify their teachings to arrive at the claimed invention. Additionally, Kehat is void of any disclosure that would have provided the skilled artisan with a reasonable expectation of success when attempting to modify the teachings of the cited art to arrive at the claimed invention.

The Office asserts that "even if there is only 1% EB efficiency when the starting ES cells is 10^5 ES cells/ml in [Dang's LSC] liquid cell culture, the resulting EB would be about 100 EBs/ml." OA, p. 12, ¶1 and p. 14, ¶3. First, the Office fails to point to any factual support in the record for its assumption that Dang's liquid suspension culture yields 1% EB efficiency at 10^5 ES cells/ml. Applicants respectfully request clarification for the factual basis supporting such assumption. 37 C.F.R. § 1.104(d)(2). Second, Dang's LSC culture is a *static* culture. Dang, ¶162. In contrast, claim 45 is directed to a method comprising, *inter alia*, rocking the container containing the liquid single cell suspension culture. Therefore, even assuming *arguendo* that an LSC culture disclosed in Dang started with a 10^5 ES cells/ml suspension results in similar EB concentrations as the claimed method, Dang does not render the claimed *method* obvious because the elements of Dang's LSC method and the elements of the method of claim 45 are radically different.

At least for the above reasons, Applicants respectfully request that the rejection under 35 U.S.C. 103(a) be reconsidered and withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the

outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

Paul A. Calvo
Attorney for Applicants
Registration No. 57,913

Date: 4/19/11

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

1332280_3.doc